UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/594,339 | 10/17/2006 | Tomoyuki Nakamura | 2006_1605A | 1266 |

513 7590 04/29/2010

WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

| EXAMINER | |
|---|---|
| SWOPE, SHERIDAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 04/29/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ddalecki@wenderoth.com
eoa@wenderoth.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/594,339 | NAKAMURA ET AL. | |
| | Examiner | Art Unit | |
| | SHERIDAN SWOPE | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27,29 and 33-46* is/are pending in the application.

4a) Of the above claim(s) *3-27,29,33,34 and 36-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' filing of January 7, 2010, in response to the action of August 7, 2009, is acknowledged. It is acknowledged that no claims have been amended, cancelled, or added. Claims 1-27, 29, and 33-46 are pending. Claims 3-27, 29, 33, 34, and 36-46 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 2, and 35 are hereby reconsidered.

### *Claim Rejections - 35 USC § 112-Second Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

For Claim 1, the phrase "an activity to bind to a human integrin selected from the group consisting of αvβ3, αvβ5, and α9β1" renders the claim indefinite. As set forth by Applicants arguments regarding the rejection of Claims 1, 2, and 35 under 35 U.S.C. 112, first paragraph, human αvβ3 integrins encompasses three variants and human α9β1 integrins encompasses five variants. It is unclear whether the phrase "an activity to bind to a human integrin selected from the group consisting of αvβ3 …" means "an activity to bind to any one of the three human αvβ3 variants" or "an activity to bind to all three human αvβ3 variants". Likewise, it is unclear whether the phrase "an activity to bind to a human integrin selected from the group consisting of …α9β1" means "an activity to bind to any one of the five human α9β1 variants" or "an activity

to bind to all five human α9β1 variants". The skilled artisan would not know the metes and bounds of the recited invention. Claims 2 and 3, as dependent from Claim 1, are indefinite for the same reason.

Any subsequent rejection, based on clarification of the above phrases and terms, will not be considered a new ground for rejection.

### *Claim Rejections - 35 USC § 112-First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### Enablement

Rejection of Claims 1, 2, and 35 under 35 U.S.C. 112, first paragraph/lack of enablement, for reasons explained in the prior actions, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The reasons these arguments are not found to be persuasive are set forth in each reply.

(A) Applicants previously argued (June 11, 2009) that Claim 1 is now directed towards a peptide which consists of an amino acid sequence having at least 90% identity to SEQ ID NO: 6, retaining a consensus Arg-Gly-Asp motif, and having binding activity for a human αvβ3, αvβ5, or α9β1 integrin that binds to full-length human dance. Applicants also argued that the specification and Nakamura et al, 2002 provide enablement for such a peptide and therefore this rejection is overcome.

(A) Reply: It is acknowledged that Claim 1 is now directed towards a peptide which consists of an amino acid sequence having at least 90% identity to SEQ ID NO: 6, retaining the consensus RGD motif and having binding activity for a human αvβ3, αvβ5, or α9β1 integrin that binds to full-length human dance.

It is acknowledged that Nakamura et al, 2002 discloses the following. That, antibodies to human α9, human αvβ3, and human αvβ5 inhibit binding, to residues 26-68 of human fibulin-5 (DANCE), of CHO cells transfected with αvβ3, αvβ5, or α9β1 integrins. However, Nakamura et al fails to disclose whether said CHO cells were transfected with human αvβ3, αvβ5, or α9β1 integrins. Therefore, Nakamura et al, 2002 does provide evidence that the peptide of SEQ ID NO: 6 or full-length human DANCE binds to any human αvβ3, αvβ5, or α9β1 integrin.

(B) The Office's action of August 7, 2009 discussed Nakamura et al, 2000, not Nakamura et al, 2002.

(B) Reply: It is acknowledged that the Office's action of August 7, 2009 did not discuss Nakamura et al, 2002. Thus, this action is non-final.

(C) Nakamura 2002 teaches DANCE (fibulin-5) binding to αvβ3, αvβ5, and α9β1 (pg 172, parg 1).

(C) Reply: It is acknowledged that Nakamura et al, 2002 teaches that DANCE serves a ligand for some αvβ3, αvβ5, or α9β1 integrins. However, Nakamura et al, 2002 does not teach whether said integrins are human or which specific splice variants bind. See (A), above.

(D) Nakamura 2002 teaches that DANCE serves as a ligand for these integrins through its amino-acid terminal domain. SEQ ID NO: 6 corresponds to the 24-77 AA in DANCE and, thus, corresponds to this amino region.

(D) Reply: It is acknowledged that SEQ ID NO: 6, consisting of residues 24-77 of human fibulin-5/DANCE, comprises the region of DANCE, residues 26-68, used by Nakamura et al, 2002. However, for the reasons explained in (A), above, Nakamura et al, 2002 cannot provide enablement for the instant claims.

(E) Reference Example 1 of the specification (starting on page 63) is, in part, directed towards DANCE with the portion corresponding to SEQ ID NO 6 deleted. Such deletion resulted in loss of binding to αvβ3, αvβ5, and α9β1 integrins.

(E) Reply: Reference Example 1 of the specification (pg 63-64) does not disclose that deletion of SEQ ID NO: 6 resulting in loss of binding, per se, of DANCE to αvβ3, αvβ5, and α9β1 integrins. Reference Example 1 of the specification (pg 63-64) does disclose that the peptide of SEQ ID NO: 6 is required for the ability of full-length DANCE to promote vascular endothelial cell adhesion. However, said pages fail to disclose if said endothelial cells are human, if said endothelial cells express any one or more of the human αvβ3, αvβ5, or α9β1 integrins, whether any of the encompassed human variants of the αvβ3, αvβ5, or α9β1 integrins bind to full-length human DANCE, or whether deletion of SEQ ID NO: 6 abolishes binding, per se, of DANCE to any human variant of the αvβ3, αvβ5, or α9β1 integrins. Thus, Reference Example 1 does not disclose that SEQ ID NO: 6, any variant thereof having 90% identity, or the full-length human DANCE binds to any human αvβ3, αvβ5, or α9β1 integrin, as recited in the instant claims.

(F) Looking at Reference Example 1, it is noted that the RGD motif appears to be important for binding to αvβ3, αvβ5, and α9β1 as a single mutation in this motif results in a large reduction in binding and deletion of this motif results in no binding. Thus, Applicants have

provided a structure to guide a person of art to practice the claimed invention without undue experimentation.

(F) Reply: It is acknowledged that a single mutation in the RGD motif results in a large reduction in vascular endothelial cell adhesion. The Examiner fails to see where Reference Example 1 shows analysis of a protein completely lacking the RGD motif.)

Moreover, said pages fail to disclose if said endothelial cells are human, if said endothelial cells express any one or more of the human αvβ3, αvβ5, or α9β1 integrins, whether any of the human variants of the αvβ3, αvβ5, or α9β1 integrins bind to full-length human DANCE, or whether the single mutation in the RGD motif affects binding, per se, of DANCE or the peptide of SEQ ID NO: 6 to any human variant of the αvβ3, αvβ5, or α9β1 integrins. Thus, Reference Example 1 does not disclose that SEQ ID NO: 6, any variant thereof having 90% identity, or the full-length human DANCE binds to any human αvβ3, αvβ5, or α9β1 integrin, as recited in the instant claims.

(G) The genus of human αvβ3, αvβ5, and α9β1 integrins is very small and highly homologous as shown by the attached references (Attachments A-H).

Fomaro et al, 1997 (pg 186, Table 1) and de Melker et al, 1999 (pg 501-2, Table 2) disclose that β1 and β3 integrins share only 4 (or 5) and 2 (or 3) cytoplasmic splice variants, respectively. Further, Fornaro et al discloses that differences in the cytoplasmic domain do not affect either αβ heterodimer formation or the ligand specificity (pg 185, Abstract). (A&B)

de Melker et al further discloses that there is one 60 kDa truncated form of β3 integrin which consists of the 404 N-terminal extracellular residues of β3 followed by 23 residues encoded by intronic sequences (pg 501, col2, lines 4-8). (B)

de Melker et al also discloses that no splice variants for human β5 integrin have been detected (pg 503, col1, lines 7-9). This is also supported by the information relating to human β5 integrin gene entered in the latest NCBI database. According to the information of ITGB5 integrin, beta 5 in the NCBI Gene database, only one human β5 integrin gene transcript, NM_002213.3, is registered (Entrez gene, 3693). The date of first entry of NM_002213 into NCBI is March 24, 1999 (Revision history) (B-D).

For human α9 integrin, only one transcript, NM_002207.2, encoding a protein NP_002198.2 is registered (Entrez gene, 3680). The date of first entry is November 23, 2000 (Revision history). (C & E).

For human αv integrin, three transcripts, NM_002210.3, NM_001145000.1 and NM_001144999.1, are registered (Entrez gene, 3685). However, the date of first entry of each sequence is March 24, 1999, February 12, 2009, and February 12, 2009, respectively, and therefore, the transcript variant for human αv integrin known before the priority date of the present application is only NM 002210.3. (C & F-H)

From the foregoing, it is clear that, prior to the filing date of the present application, 4 (or 5) and 2 (or 3) kinds of cytoplasmic splice variants were known for human β1 and β3 integrins, respectively; in addition, it was considered that differences in the cytoplasmic domain do not affect the ligand specificity, only one kind of a truncated form having different extracellular domain was known for human β3 integrin, and only one kind of transcript was known for human β3, α9, and αv integrins. Therefore, at the time of filing, the genus of human αvβ3, αvβ5, and α9β1 integrins was very small and highly homologous.

(G) Reply: It is acknowledged that, based on the above references, there was one variant of each of αv, α9, and β5, three variants of β3, and five variants of β1 at the time of filing. Thus, αvβ3 encompasses 1 x 3=3 variants, αvβ5 encompasses 1 x 1=1 variant, and α9β1 encompasses 1 x 5=5 variants; for a total of nine human variants. However, the Examiner fails to see that either the specification or the prior art teach which, if any of said nine human variants binds the polypeptide of SEQ ID NO: 6, any variant thereof having at least 90% identity to SEQ ID NO: 6, or full-length human DANCE, as recited in the instant claims.

For these reasons and those explained in the prior actions, rejection of Claims 1, 2, and 35 under 35 U.S.C. 112, first paragraph/lack of enablement, is maintained.

**Written Description**

Rejection of Claims 1, 2, and 35 under 35 U.S.C. 112, first paragraph/written description, for the reasons explained in the prior actions, is maintained. In support of their request that said rejection be withdrawn, Applicants argue the following. That, as noted above [Enablement], the specification sets forth that the RGD motif appears to be important for binding to the claimed integrins as a single mutation in this motif results in a large reduction in binding and deletion of this motif results in no binding. Further, the present application and Nakamura 2002 together demonstrate that SEQ ID NO: 6 can bind αvβ3, αvβ5, and α9β1. Also, the attached references show that the genus of these integrins known at the time of filing was very small. Thus, Applicants respectfully suggest that the teachings in the specification and the knowledge in the art indicate that Applicants had possession of the claimed invention at the time of filing. These arguments are not found to be persuasive for the reasons stated above [Enablement].

Rejection of Claim 1, 2, and 35 under 35 U.S.C. 112, first paragraph/written description/new matter, because Claim 1 introduces the limitation of "having an activity to bind to a human integrin selected from the group consisting of αvβ3, αvβ5, or α9β1, which integrin is capable of binding to full length human DANCE polypeptide", is maintained. In support of their request that said rejection be withdrawn, Applicants argue the following. With regard to the limitation "having an activity to bind to a human integrin selected from the group consisting of αvβ3, αvβ5, and α9β1, which integrin is capable of binding to a full length human DANCE polypeptide", it is noted the support for such phrase can be found on page 63, line 20 to page 64, line 1 of the specification and Nakamura 2002 which is incorporated into the specification by reference.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that the specification (pg 63-64) discloses that the peptide of SEQ ID NO: 6 and the RGE motif therein are required for the ability of DANCE to promote vascular endothelial cell adhesion. However, said pages fail to disclose if said endothelial cells are human, if said endothelial cells express any one or more of the human αvβ3, αvβ5, or α9β1 integrins, whether any of the encompassed human variants of the αvβ3, αvβ5, or α9β1 integrins bind to full-length human DANCE, or whether deletion of SEQ ID NO: 6 or mutation of RGE affects binding, per se, of DANCE to any human variant of the αvβ3, αvβ5, or α9β1 integrins. Thus, Reference Example 1 does not disclose that SEQ ID NO: 6, any variant thereof having 90% identity, or the full-length human DANCE binds to any human αvβ3, αvβ5, or α9β1 integrin, as recited in the instant claims.

For these reasons and those explained in the prior actions, rejection of Claims 1, 2, and 35 under 35 U.S.C. 112, first paragraph/written description, is maintained.

***Allowable Subject Matter***

No claims are allowable.

**Final Comments**

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652